REMARKS

Claims 20-33 and 42-54 were pending in the subject application. Applicants have hereinabove amended claims 30 and added new claim 55. Support for the amendment to claim 30 may be found, *inter alia*, in the specification at page 13, lines 3-8 and 35-37 and page 61, lines 3-8. Support for new claim 55 may be found, *inter alia*, in the specification at page 13, lines 3-8 and 35-37 and page 61, lines 3-8. Applicants maintain that these amendments raise no issue of new matter. Upon entry of this amendment, claims 20-33 and 42-55 will be pending and under examination.

Declaration Under 37 C.F.R. §1.132

The Examiner indicated on page 2 of the December 4, 2008 Final Office Action that the Declaration of Dr. Harold Wanebo has been received and entered into the record. The Examiner further noted that the declaration has not been considered because it is incomplete. Specifically, the Examiner noted that pages 3 and 4 of the Declaration are missing and as such it is not clear what experiments resulted in the data presented in Exhibits B-G. The Examiner further noted that the Examiner relied on the discussion of the data presented in Exhibits B-g as presented in Applicant's remarks at pages 14-17 of the Amendment filed August 15, 2008.

In response, applicants attach hereto as **Exhibit 1**, a copy of the signed declaration of Dr. Harold Wanebo, including pages 3-4. Applicants note that pages 3 and 4 were inadvertently non submitted with the Declaration filed August 15, 2008.

Withdrawn Rejections

Applicants acknowledge that the Examiner has withdrawn the rejection of claims 20, 25, and 31 under 35 U.S.C. §103 was being unpatentable over Jayadev et al. in view of Mycek et al.

Applicants acknowledge that the Examiner has withdrawn the rejection of claims 20-29 and 31-33 under 35 U.S.C. §103 as being unpatentable over

Spencer et al. in view of Cai et al.

Allowable Subject Matter

The Examiner indicated on page 5 of the December 4, 2008 Final Office Action that claims 20-29, 31-33 and 42-54 are allowable.

Rejections Under 35 U.S.C. §103

The Examiner maintained the rejection of claim 30 under 35 U.S.C. §103 as being allegedly unpatentable over Jayadev et al. in view of Mycek et al. The Examiner also maintained the rejection of claim 30 as allegedly being unpatentable over Spencer et al. in view of Cai et al.

In response, applicants respectfully traverse the Examiner's ground of rejection. Nevertheless, without conceding the correctness of the Examiner's rejection, applicants note that claim 30 has been amended hereinabove and claim 55 has been added. Applicants will address the Examiner's comments with respect to amended claim 30 and new claim 55.

Applicants' invention, as recited in amended claim 30, provides a pharmaceutical composition comprising paclitaxel, C_6-ceramide and a pharmaceutically acceptable carrier, wherein the amount of paclitaxel and the amount of C_6-ceramide in combination are effective to induce at least a 50% growth inhibition of a tumor comprising head and neck squamous carcinoma cells.

Applicants' invention, as recited in new claim 55, provides a pharmaceutical composition comprising paclitaxel, C_6-ceramide and a pharmaceutically acceptable carrier, wherein the amount of paclitaxel and the amount of C_6-ceramide in combination are effective to induce at least a 50% growth inhibition of a tumor comprising pancreatic cancer cells.

Claim 30(Head and Neck Squamous Carcinoma Cells)

Jayadev et al. disclose that C_6-ceramide induces a significant block in

cell cycle progression accompanied by apoptosis in Molt-4 human leukemia cells. Jayadev et al. do not disclose the use of paclitaxel, or any use of any other chemotherapeutic agent in combination with C_6-ceramide.

Mycek et al. disclose paclitaxel as a chemotherapeutic agent in combination therapy with other anticancer agents, but do not disclose C_6-ceramide as a possible anticancer agent. Mycek et al. disclose that paclitaxel has shown good activity against advanced ovarian cancer and metastatic breast cancer and has shown favorable results in small-cell lung cancer, squamous-cell carcinoma of the head and neck and "several other cancers". While Mycek et al. disclose that the combination therapy of paclitaxel with other anticancer drugs is being evaluated, they do not disclose the specific combination of paclitaxel with C_6-ceramide.

None of Jayadev et al. or Mycek et al. disclose that C_6-ceramide inhibits growth of head and neck squamous carcinoma cells, or a pharmaceutical composition comprising paclitaxel, C_6-ceramide and a pharmacetucically acceptable carrier, wherein the amount of C_6-ceramide is effective to induce at least 50% growth inhibition of a tumor comprising head and neck squamous carcinoma cells (amended claim 30). Moreover, neither of these references disclose any expected results of combination therapy with paclitaxel and C_6-ceramide. Therefore the combination of Jayadev et al. with Mycek et al. does not render obvious applicants invention as recited in claim 30.

With respect to the rejection under 103(a) of Spencer et al. in view of Cai et al., applicants note that Spencer et al. disclose paclitaxel as an anticancer agent with broad-spectrum anticancer activity, including breast carcinoma, colon carcinoma, head and neck squamous cell carcinoma, leukemia, pancreatic carcinoma and prostate cancer. Spencer et al. further disclose combination therapy comprising paclitaxel and several other anticancer agents, but do not disclose combination therapy with C_6-ceramide. Spencer et al. do not disclose C_6-ceramide

as an anticancer agent.

Cai et al. teach C_6-ceramide induces apoptosis in both TNF-sensitive and TNF-resistant breast cancer cells, but does not teach the combination of C_6-ceramide with paclitaxel or any other anticancer agent. Therefore, applicants maintain that the combination of Spencer et al. with Cai et al. does not render obvious applicants' claimed invention.

None of Spencer et al. or Cai et al. disclose that C_6-ceramide inhibits growth of head and neck squamous carcinoma cells, or a pharmaceutical composition comprising paclitaxel, C_6-ceramide and a pharmacetucically acceptable carrier, wherein the amount of C_6-ceramide is effective to induce at least 50% growth inhibition of a tumor comprising head and neck squamous carcinoma cells (amended claim 30). Moreover, neither of these references disclose any expected results of combination therapy with paclitaxel and C_6-ceramide. Therefore the combination of Spencer et al. with Cai et al. does not render obvious applicants invention as recited in claim 30.

In view of the above remarks, applicants maintain that the combination of either Jayadev et al. in view of Mycek et al. or Spencer et al. in view of Cai et al. does not render applicants' claimed invention obvious. Specifically, even if the Examiner has established a prima facie case of obviousness, to which applicants do not concede, applicants maintain that the specification discloses that paclitaxel in combination with C_6-ceramide produce unexpected results.

Specifically, page 51 of the instant specification discloses, *inter alia*, that Tu138 (head and neck squamous carcinoma cells) were implanted subcutaneously in nude mice, i.e. *in vivo*, which were treated beginning of day 4 with thrice weekly injections of paclitaxel 120 µg/0.1ml, alone, C_6-ceramide, 500 µg in 0.2ml, alone, combinations thereof and control. As shown in Figures 11 and 12, tumor growth was significantly inhibited by combination of paclitaxel and ceramide. For

example, in Figure 11, after five weeks of treatment, the average size of tumor was just over 50 $(mm)^2$ in the case of treatment with combination paclitaxel and C_6-ceramide. In contrast, the average size of tumor was just under 100 $(mm)^2$ for C_6-ceramide alone and just under 250 $(mm)^2$ for paclitaxel alone. In addition, the specification discloses that in human Tu138 head and neck squamous carcinoma cells lines, paclitaxel in combination with C_6-ceramide inhibited growth of the Tu138 cells by 66% as compared to growth inhibition of only 10% and 28% upon administration of each of paclitaxel and C_6-ceramide alone.

Accordingly, applicants have demonstrated *in vivo* an unexpected effect on growth inhibition of head and neck squamous carcinoma cells with the combination of paclitaxel and C_6-ceramide.

Applicants maintain that the unexpected results further render unobvious applicants' invention as recited in amended claim 30 over Jaydev et al. in view of Mycek et al. and also over Spencer et al. in view of Cai et al.

Furthermore, as noted above, the Examiner has indicated that claims 20-29 and 31-33 are allowable, all of which are directed to the combination of paclitaxel and C_6-ceramide for use in methods to inhibit growth of a tumor comprising head and neck squamous carcinoma cells (claim 20 and dependent claims thereof), methods of decreasing the size of a tumor comprising tumor cells, wherein the tumor cells are head and neck squamous cell carcinoma cells (claim 25 and dependent claims thereof) and methods for treating a subject afflicted with head and neck squamous cell cancer (claim 31 and dependent claims thereof). In view of the allowability of these claims, applicants maintain that claim 30, which has been amended hereinabove to recite, in relevant part, "head and neck squamous carcinoma cells", is also allowable.

In view of these remarks, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection under 35 U.S.C. §103 with respect to claim 30.

Claims 55 (Pancreatic Cancer Cells)

Applicants have hereinabove added new claim 55. Applicant will address the Examiner's rejection of claim 30 with respect to new claim 55.

As noted above, Jayadev et al. disclose that C_6-ceramide induces a significant block in cell cycle progression accompanied by apoptosis in Molt-4 human leukemia cells. Jayadev et al. do not disclose the use of paclitaxel, or any use of any other chemotherapeutic agent in combination with C_6-ceramide.

Mycek et al. disclose paclitaxel as a chemotherapeutic agent in combination therapy with other anticancer agents, but do not disclose C_6-ceramide as a possible anticancer agent. Mycek et al. disclose that paclitaxel has shown good activity against advanced ovarian cancer and metastatic breast cancer and has shown favorable results in small-cell lung cancer, squamous-cell carcinoma of the head and neck and "several other cancers". While Mycek et al. disclose that the combination therapy of paclitaxel with other anticancer drugs is being evaluated, they do not disclose the specific combination of paclitaxel with C_6-ceramide. Mycek et al. do not disclose paclitaxel as therapy for pancreatic cancer.

None of Jayadev et al. or Mycek et al. disclose that C_6-ceramide inhibits growth of pancreatic cancer cells, or a pharmaceutical composition comprising paclitaxel, C_6-ceramide and a pharmacetucically acceptable carrier, wherein the amount of C_6-ceramide is effective to induce at least 50% growth inhibition of a tumor pancreatic cancer cells (new claim 55). Moreover neither reference discloses paclitaxel for use in treating pancreatic cancer. Finally, neither of these references disclose any expected results of combination therapy with paclitaxel and C_6-ceramide. Therefore the combination of Jayadev et al. with Mycek et al. does not render obvious applicants invention as recited in new claim 55.

With respect to the rejection under 103(a) of Spencer et al. in view of Cai et al., applicants note that Spencer et al. disclose paclitaxel as an anticancer agent with broad -spectrum anticancer activity, including breast carcinoma, colon carcinoma, head and neck squamous cell carcinoma, leukemia, pancreatic carcinoma and prostate cancer. Spencer et al. further disclose combination therapy comprising paclitaxel and several other anticancer agents, but do not disclose combination therapy with C_6-ceramide. Spencer et al. do not disclose C_6-ceramide as an anticancer agent.

Cai et al. teach C_6-ceramide induces apoptosis in both TNF-sensitive and TNF-resistant breast cancer cells, but does not teach the combination of C_6-ceramide with paclitaxel or any other anticancer agent. Therefore, applicants maintain that the combination of Spencer et al. with Cai et al. does not render obvious applicants' claimed invention.

None of Spencer et al. or Cai et al. disclose that C_6-ceramide inhibits growth of pancreatic cancer cells, or a pharmaceutical composition comprising paclitaxel, C_6-ceramide and a pharmacetucically acceptable carrier, wherein the amount of C_6-ceramide is effective to induce at least 50% growth inhibition of a tumor comprising pancreatic cancer cells (new claim 55). Moreover, neither of these references disclose any expected results of combination therapy with paclitaxel and C_6-ceramide. Therefore the combination of Spencer et al. with Cai et al. does not render obvious applicants invention as recited in new claim 55.

In addition, applicants maintain that the specification discloses that paclitaxel in combination with C_6-ceramide produce unexpected results.

Specifically, the specification discloses on page 52, in Table 2, that in RWP-2 human pancreatic cell lines, paclitaxel and C_6-ceramide inhibited growth of the RWP-2 cells bys 75% as compared to growth

inhibition of only 2% and 6% with administration of each of the agents alone, respectively.

In further support of unexpected results, applicants attach hereto as **Exhibit 1** a Declaration Under 37 C.F.R. §1.132 of Dr. Harold Wanebo, M.D., a co-inventor named in the subject application. In the Declaration, Dr. Wanebo declares the following:

1. That he and/or Shashikant Mehta and/or individuals acting under their direction performed the following *in vivo* experiments to test the combined effects of paclitaxel ("taxol") and C_6-ceramide. SCID/Beige/Taconic male mice (22-25 grams, 6-8 weeks old) (Taconic Laboratory, Germantown, NY, USA) were each inoculated with 2 x 10^6 L3.6 human pancreatic adenocarcinoma ("PA") cells subcutaneously in the internal surface of the right thigh. Four days later, when the mice developed primary tumors, chemotherapy was commenced by injecting the mice intra-peritoneally with C_6-ceramide (also referred to as "ceramide 6") (10.0 mg/kg) alone (Group 2), taxol, i.e. paclitaxel (3.0 mg/kg) alone (Group 3), oxaliplatin (2.5 mg/kg) alone (Group 4), cis-platinum (also referred to as "cisplatin") (2.5 mg/kg) alone (Group 5), or combinations of taxol and C_6-ceramide (Group 6), oxaliplatin and C_6-ceramide (Group 7), and cis-platinum and C_6-ceramide (Group 8). The control group (Group 1) contained mice receiving no chemotherapeutic agent. The mice were treated 3 times per week for 4 weeks, and were observed for 6 weeks after commencing chemotherapy. The experimental results discussed below are those obtained with respect to Groups 1, 2, 3 [sic], and 6 [sic], even though data with respect to the remaining Groups are shown in the Exhibits annexed hereto.

2. Survival percentage rates among mice in Groups 1-8 were determined. As shown in **EXHIBIT B**, all mice in the control group (Group 1) died by the third week. All mice receiving

C_6-ceramide alone (Group 2) died by the fourth week. All mice receiving taxol alone (Group 3) died by the fourth week of observation. In contrast, 60% of the mice receiving a combination of taxol and C_6-ceramide (Group 6) were still alive as of the sixth week.

3. Mean survival times ("MST") among the mice in Groups 1-8 were determined. As shown in **EXHIBIT C**, the mice in the control group (Group 1) had a MST of approximately 17.8 days; the mice receiving C_6-ceramide alone (Group 2) had a MST of approximately 20.8 days; the mice receiving taxol alone (Group 3) had a MST of approximately 23.0 days; and the mice receiving a combination of taxol and C_6-ceramide (Group 6) had a MST of approximately 35.2 days.

4. Tumor volumes among the mice in Groups 1-8 were determined. As shown in **EXHIBIT D**, the mice in the control group (Group 1) had tumors with a mean tumor volume ("MTV") of approximately 1.56 cm^3; the mice receiving C_6-ceramide alone (Group 2) had tumors with a MTV of approximately 1.69 cm^3; the mice receiving taxol alone (Group 3) had tumors with a MTV of approximately 1.83 cm^3; and the mice receiving a combination of taxol and C_6-ceramide (Group 6) had tumors with a MTV of approximately 1.19 cm^3.

5. The mean rate of tumor development ("MRTD"), which indicates the speed of tumor development, was measured among the mice in Groups 1-8 using the formula MTV/MST. As shown in **EXHIBIT E**, the mice in the control group (Group 1) had a MRTD of approximately 0.086 cm^3/day; the mice receiving C_6-ceramide alone (Group 2) had a MRTD of approximately 0.082 cm^3/day; the mice receiving taxol alone (Group 3) had a MRTD of approximately 0.078 cm^3/day; and the mice receiving a combination of taxol and C_6-ceramide (Group 6) had a MRTD of approximately 0.035 cm^3/day.

6. The mean weight of tumor ("MWT") among the mice in Groups 1-8 was determined. As shown in **EXHIBIT F**, the mice in the control group (Group 1) had a MWT of approximately 1.56 grams; the mice receiving C_6-ceramide alone (Group 2) had a MWT of approximately 1.04 grams; the mice receiving taxol alone (Group 3) had a MWT of approximately 0.82 grams; and the mice receiving a combination of taxol and C_6-ceramide (Group 6) had a MWT of approximately 1.26 grams.

7. Mean body weight ("MBW") was measured every week for the mice in Groups 1-8. As shown in **EXHIBIT G**, the mice in the control group (Group 1) had a MBW of approximately 17.2 grams; the mice receiving C_6-ceramide alone (Group 2) had a MBW of approximately 17.0 grams; the mice receiving taxol alone (Group 3) had a MBW of approximately 17.4 grams; and the mice receiving a combination of taxol and C_6-ceramide (Group 6) had a MBW of approximately 20.0 grams.

As shown in **Exhibit B**, mice receiving paclitaxel (taxol) alone or C_6 ceramide alone all died by the fourth week of treatment. In contrast, 60% of mice were still alive after 6 weeks of treatment when paclitaxel and C_6-ceramide were administered in combination. Moreover, as shown in **Exhibit C**, the mean survival time of mice receiving control treatment was 17.8 days. Mice receiving paclitaxel (taxol) alone had a mean survival time of 20.8 days and mice receiving C_6-ceramide alone has a mean survival time of 23.0 days. In contrast, mice receiving a combination of paclitaxel and C_6-ceramide had a mean survival time of 35.2 days. In addition, the mean rate of tumor development (cm3/day), as shown in **Exhibit D**, was 0.086 for mice receiving control treatment. Mice receiving C_6-ceramide alone was 0.082 and 0.078 for mice receiving paclitaxel alone. In contrast, the mean rate of tumor development in mice receiving a combination of paclitaxel and C_6-ceramide was 0.035. In addition, the specification discloses on page 52, in Table 2, that in RWP-2 human pancreatic cell lines, paclitaxel

and C_6-ceramide inhibited growth of the RWP-2 cells bys 75% as compared to growth inhibition of only 2% and 6% with administration of each of the agents alone, respectively.

Accordingly, applicants have demonstrated *in vivo* an unexpected effect on growth inhibition of pancreatic cancer cells with the combination of paclitaxel and C_6-ceramide.

Applicants maintain these unexpected results further render nonobvious the applicants' invention, as recited in new claim 55, over Jayadev et al. in view of Mycek et al. and also over Spencer et al. in view of Cai et al.

Furthermore, as noted above, the Examiner has indicated that claims 42-54 are allowable, all of which are directed to the combination of paclitaxel and C_6-ceramide for use in methods to inhibit growth of a tumor comprising pancreatic cancer cells (claim 42 and dependent claims thereof), methods of decreasing the size of a tumor comprising tumor cells, wherein the tumor cells are pancreatic cancer cells (claim 47 and dependent claims thereof) and methods for treating a subject afflicted with pancreatic cancer (claim 52 and dependent claims thereof). In view of the allowability of these claims, applicants maintain that new claim 55, which recites, in relevant part, "pancreatic cancer cells", is also allowable.

In view of the preceding remakrs, applicants respectfully submit that new claim 55 is non-obvious over Jayadev et al. in view of Mycek et al. and also over Spencer et al. in view of Cai et al.

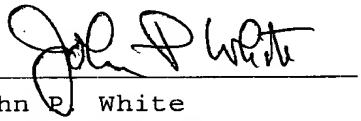
Conclusion

In view of the remarks hereinabove, applicants respectfully submit that the grounds of rejection set forth in the December 4, 2008 Final Office Action have been overcome. Applicants respectfully solicit a notice of allowance.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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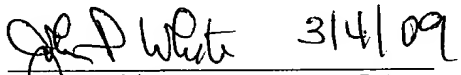

3/4/09

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EXHIBIT 1

Applicants: Harold J. Wanebo and Shashikant Mehta
U.S. Serial No.: 09/287,884
Filed: April 7, 1999